0021-972X/95/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 80, No. 6
Printed in U.S.A.

Somatostatin Enhances Insulin-Stimulated Glucose Uptake in the Perfused Human Forearm

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ABSTRACT

Somatostatin is widely used in experimental metabolic studies to control hormone actions. It has also been suggested that, in addition to its well known suppressive effects, somatostatin *per se* may increase insulin sensitivity.

In order to examine this suggestion, we gave six healthy male volunteers (age 33 ± 1 yr, mean ± SEM; body mass index, 24.1 ± 0.6 kg/m^2) either a local intraarterial (brachial artery) or a systemic venous infusion of 25 μg/h somatostatin twice. The study consisted of a 1-h basal period and a 2-h systemic hyperinsulinemic (0.4 mU/kg·min) euglycemic clamp.

Compared with the systemic control infusion, local forearm perfusion with somatostatin caused a 55% increase in insulin-stimulated forearm glucose uptake (0.74 ± 0.18 *vs.* 0.47 ± 0.19 mmol/L, $P < 0.05$). Intraarterial somatostatin perfusion did not alter basal forearm glucose uptake (0.14 ± 0.07 *vs.* 0.17 ± 0.12 mmol/L), the amount of glucose administered during the clamp (M-value, 3.2 ± 0.5 *vs.* 3.0 ± 0.6 mg/kg·min), or the levels of insulin, C-peptide, glucagon, or GH. Intermediary metabolite exchange across the forearm, total forearm blood flow, and oxygen saturations also remained stable. Glucose concentrations were slightly higher (0.06 ± 0.01 mmol/L) in arterial than in arterialized blood, whereas lactate concentrations were comparatively decreased (108 ± 51 μmol/L) in arterial blood.

Our data suggest that somatostatin increases insulin-stimulated muscle utilization of glucose through local mechanisms. Although the nature of this increase remains to be established, it should be taken into consideration in metabolic studies using somatostatin. (*J Clin Endocrinol Metab* 80: 1789–1793,1995)

SOMATOSTATIN-14 has gained wide experimental use ever since the original observation that the peptide inhibits insulin secretion in humans (1). In order to segregate primary metabolic events from effects that are secondary to changes in hormone levels, somatostatin (SRIF) may be infused alone to clamp insulin, glucagon, and GH levels or in combination with adrenergic blockers and glucocorticoid synthesis inhibitors to further ensure control of catecholamine and cortisol action (2, 3).

Interpretation of metabolic studies employing somatostatin is complicated by various factors. First, somatostatin may act to decrease splanchnic blood flow, to suppress release of gut hormones (the metabolic significance of which is largely unknown), and to delay gastrointestinal absorption (4, 5). Second, studies in which hormones such as insulin, glucagon, or GH are coinfused to recreate a desired hormonal profile invariably fail to reproduce the exact anatomical site of hormone release (*e.g.* the portal bed) or the intricate pattern of pulsatile hormone secretion and the molecular mixture of variously sequenced peptides that are released. Third, the question of whether somatostatin *per se* may potentiate the actions of insulin on glucose metabolism remains unanswered. Some studies employing systemic infusion of somatostatin have reported such an insulin-augmenting effect on peripheral disposal of glucose (6–10), whereas others have not (11, 12). The outcome of such studies will be critically dependent on whether hormone replacement during somatostatin infusion did in fact appropriately mimic the initial conditions as intended.

It is fundamental to the interpretation of many investigations using SRIF that SRIF has no direct effects on glucose metabolism. In order to clarify this, the present study was designed to determine any possible immediate local effects of somatostatin on basal and insulin-stimulated substrate metabolism in the human forearm. To circumvent the numerous indirect effects of somatostatin mentioned above, the peptide was perfused directly into the brachial artery and was compared with a systemic control infusion.

Materials and Methods

Subjects and design

Six healthy, normal-weight male volunteers (age 33 ± 1 yr; body mass index, 24.1 ± 0.6 kg/m^2) gave informed consent to participate in the study, which had been approved by the local ethical committee. After an overnight fast of 10 h, the subjects were studied in the supine position while in the hospital. All subjects ingested a weight-maintaining diet containing at least 200 g of carbohydrate for 3 days before the studies, and all were studied twice in random order from 0830 h until 1200 h. At 0900 h, an intraarterial (brachial artery) infusion of either somatostatin-14 (Ferring AB, Malmø, Sweden) or saline was begun at a rate of 5 mL/h and continued for the following 3 h. During the saline studies, identical solutions of somatostatin were infused iv in the contralateral arm. For the infusions, 100 μg somatostatin was dissolved in 20 mL saline, corresponding to an infusion rate of 25 μg/h. At 1000 h, a 2-h systemic euglycemic hyperinsulinemic glucose clamp was started for the purpose of reaching plasma glucose concentrations 0.15 mmol/L below ambient glycemia. Insulin was infused at a rate of 0.4 mU/kg·min, and euglycemia was maintained by infusion of 10% glucose on the basis of frequent analysis of plasma glucose concentrations in arterialized blood, as described previously (13).

Received October 4, 1994. Revision received December 20, 1994. Accepted December 29, 1994.

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Appendix A for 09/507,081

Catheters

At 0815 h, a short teflon 5F catheter was inserted percutaneously into the brachial artery of the left arm under local anesthesia and was advanced 10 cm proximal to the level of the elbow. This catheter was used for infusion of either saline or SRIF. Catheters for infusions and for measurements of forearm arteriovenous substrate balances were placed, as described previously (14). One catheter was inserted retrogradely into a heated dorsal hand vein of the right hand (for sampling of arterialized blood), a second catheter was placed retrogradely in a deep antecubital vein of the left arm (adjacent to the arterial line for sampling of deep venous blood), and a third catheter was inserted in an antecubital vein of the heated right arm for infusions of insulin, glucose, and either saline or SRIF. Before each deep venous blood sample was taken, hand blood flow was interrupted by inflating a wrist cuff to a pressure of 250 mm Hg.

Measurements

Total forearm blood flow was measured by a strain gauge, mercury in rubber, venous occlusion plethysmographic method (14). Forearm substrate exchange is given as arteriovenous differences.

Plasma glucose was measured on a glucose analyzer (Beckman Instruments, Palo Alto, CA) immediately after sampling. Blood lactate, alanine, 3-hydroxybutyrate (3-OHB), and glycerol were assayed by an automated fluorimetric method (15). Serum free fatty acids (FFAs) were measured radiochemically (16). Radioimmunoassays were used to measure plasma glucagon and serum GH and insulin (17). Serum C-peptide was assayed using a commercial kit (Immunonuclear Corp., Stillwater, MN).

Blood samples of arterialized and deep venous blood were drawn at the time points indicated in the Figures: at −10 and 0 min (before SRIF); at 20, 40, 50, and 60 min during SRIF infusion; and at 80, 100, 120, 140, 160, 170, and 180 min during the 2-h glucose clamp. The arterial infusion was discontinued briefly at the end of the 30-min baseline period, the 1-h infusion period, and the 2-h clamp, allowing for simultaneous sampling from arterial, arterialized, and deep venous blood.

Results are given as mean ± SEM. Statistical significance was assessed with analysis of variance for two repeated measures (time and treatment), and a significance level of 0.05 was employed. Where appropriate, Student's *t* tests were used to compare arteriovenous differences obtained with arterial blood at the end of the 30-min preperiod, the 1-h somatostatin infusion, and the 2-h clamp.

Unless specified otherwise, the circulating concentrations referred to below were obtained with arterialized blood. Values measured during intraarterial infusion with somatostatin are denoted SRIF, and those measured during intraarterial infusion with saline are denoted SALINE.

Results

Hormones (Table 1)

Baseline concentrations of insulin (SRIF, 95.8 ± 18.7 pmol/L; SALINE, 77.8 ± 15.1 pmol/L), C-peptide (SRIF, 400 ± 73 pmol/L; SALINE, 420 ± 53 pmol/L), GH (SRIF, 0.78 ± 0.56 μg/L; SALINE, 2.31 ± 2.00 μg/L), and glucagon (SRIF, 53 ± 6 ng/L; SALINE, 55 ± 5 ng/L) were similar ($P > 0.05$).

During the 1-h somatostatin infusion period, a small but consistent ($P < 0.05$ in all cases) decline was found in circulating levels of insulin (SRIF, 54.0 ± 13.7 pmol/L; SALINE, 33.1 ± 8.6 pmol/L), C-peptide (SRIF, 311 ± 60 pmol/L; SALINE, 285 ± 26 pmol/L), GH (SRIF, 0.17 ± 0.07 μg/L; SALINE, 0.58 ± 0.33 μg/L), and glucagon (SRIF, 42 ± 5 ng/L; SALINE, 36 ± 4 ng/L). There was no difference between any of these declines in the two groups ($P > 0.05$).

During the last hour of the clamp, comparable insulin levels were recorded (SRIF, 301 ± 39 pmol/L; SALINE, 273 ± 25 pmol/L; $P > 0.05$). Concentrations of C-peptide (SRIF, 225 ± 40 pmol/L; SALINE, 205 ± 23 pmol/L) and glucagon (SRIF, 28 ± 4 ng/L; SALINE, 27 ± 4 ng/L) continued to decline ($P < 0.05$), whereas GH remained stable (SRIF, 0.09 ± 0.03 μg/L; SALINE, 0.06 ± 0.02 μg/L). No differences were observed between these values in the two protocols ($P > 0.05$).

Glucose metabolism (Fig. 1 and Table 1)

Before infusion of somatostatin, similar plasma glucose values (SRIF, 4.94 ± 0.12 mmol/L; SALINE, 5.04 ± 0.19 mmol/L) and arteriovenous glucose gradients (SRIF, 0.11 ± 0.07 mmol/L; SALINE, 0.12 ± 0.03 mmol/L) were measured. During infusion of somatostatin, plasma glucose increased ($P < 0.05$) slightly in both situations (SRIF, 5.34 ± 0.13 mmol/L; SALINE, 5.29 ± 0.10 mmol/L), whereas the arteriovenous differences remained stable (SRIF, 0.14 ± 0.07 mmol/L; SALINE, 0.17 ± 0.12 mmol/L).

During the clamp, plasma glucose values were constant and comparable (SRIF, 5.15 ± 0.07 mmol/L; SALINE, 5.20 ± 0.09 mmol/L) (Fig. 1). The amount of exogenous glucose (M-value) necessary to maintain these glucose levels was similar (SRIF, 3.2 ± 0.5 mg/kg·min; SALINE, 3.0 ± 0.6 mg/kg·min). Forearm arteriovenous differences increased ($P < 0.05$) in both groups; however, the increase was 55% greater ($P < 0.05$) with intraarterial somatostatin (SRIF, 0.74 ± 0.18 mmol/L; SALINE, 0.47 ± 0.19 mmol/L).

Blood levels of lactate (SRIF, 634 ± 30 μmol/L; SALINE, 677 ± 56 μmol/L) and alanine (SRIF, 249 ± 15 μmol/L; SALINE, 214 ± 15 μmol/L) were stable and similar in both studies. Likewise, forearm uptake of lactate (SRIF, 30 ± 65

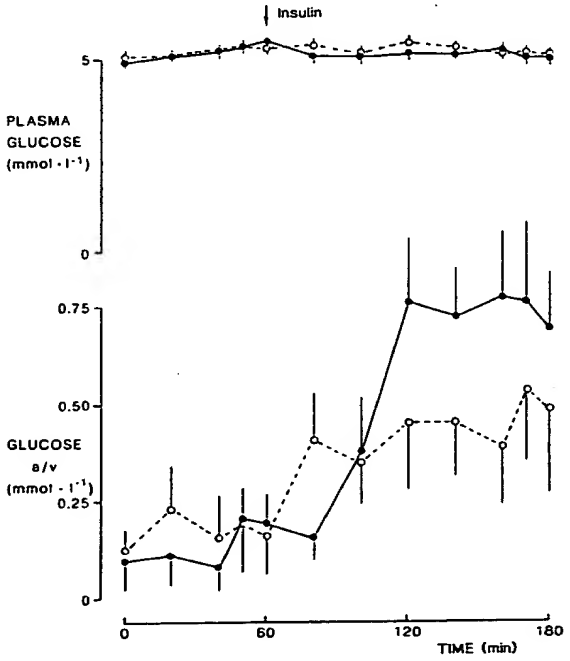

FIG. 1. Plasma glucose concentrations and arteriovenous glucose differences during intraarterial infusion of somatostatin (●–●) and saline (○–○). Somatostatin infusion was started at 0 min, and a euglycemic clamp was started at 60 min.

TABLE 1. Serum insulin, C-peptide, and FFA and plasma glucose and glucose arteriovenous concentrations and M-values and forearm blood flows during a 10-min baseline period, at the end of a 60-min SRIF infusion, and at the end of a 120-min glucose clamp

		Serum insulin (pmol · L^{-1})	Serum C-peptide (pmol · L^{-1})	Plasma glucose (mmol · L^{-1})	Glucose arteriovenous (mmol · L^{-1})	Serum FFA (μmol · L^{-1})	M-value (mg/kg · min)	Blood flow (ml/100 mL · min)
Baseline (−10–0 min)	SRIF	95.8 ± 18.7	400 ± 73	4.94 ± 0.12	0.11 ± 0.07	492 ± 54		2.9 ± 0.7
	Saline	77.8 ± 15.1	420 ± 53	5.04 ± 0.19	0.12 ± 0.03	671 ± 51		3.0 ± 0.8
SRIF infusion (0–60 min)	SRIF	54.0 ± 13.7	311 ± 60	5.34 ± 0.13	0.14 ± 0.07	768 ± 39		3.2 ± 0.6
	Saline	33.1 ± 8.6	285 ± 26	5.29 ± 0.10	0.17 ± 0.12	958 ± 67		3.4 ± 0.5
Clamp (60–180 min)	SRIF	301 ± 39	225 ± 40	5.15 ± 0.07	0.74 ± 0.18*	52 ± 20	3.2 ± 0.5	3.4 ± 0.6
	Saline	273 ± 25	205 ± 23	5.20 ± 0.09	0.47 ± 0.19	150 ± 86	3.0 ± 0.6	3.5 ± 0.7

SRIF denotes experiments in which SRIF was perfused locally in the brachial artery and saline was infused systemically and SALINE denotes the vice versa situation.

* P value less than 0.05 when SRIF is compared with Saline.

μmol/L; SALINE, 69 ± 61 μmol/L) and release of alanine (SRIF, 22 ± 12 μmol/L; SALINE, 16 ± 12 μmol/L) remained unchanged.

Lipid metabolism

All lipid parameters were statistically indistinguishable in the two experimental situations ($P > 0.05$).

Serum levels of FFA shared similar behavior: baseline values (SRIF, 492 ± 54 μmol/L; SALINE, 671 ± 51 μmol/L) increased slightly during the 1-h somatostatin infusion (SRIF, 768 ± 39 μmol/L; SALINE, 958 ± 67 μmol/L) and decreased during the clamp (SRIF, 52 ± 20 μmol/L; SALINE, 150 ± 86 μmol/L). A small comparable and constant forearm uptake of FFA was observed throughout the baseline period and during somatostatin infusion (SRIF, 44 ± 45 μmol/L; SALINE, 73 ± 32 μmol/L). During the clamp, FFA uptake declined in both cases (SRIF, −16 ± 43 μmol/L; SALINE, 10 ± 10 μmol/L) (Table 1).

Concentrations of 3-OHB were low and mirrored FFA: baseline (SRIF, 25 ± 11 μmol/L; SALINE, 39 ± 9 μmol/L), somatostatin infusion (SRIF, 48 ± 20 μmol/L; SALINE, 91 ± 20), and clamp (SRIF, 5 ± 1 μmol/L; SALINE, 7 ± 1 μmol/L). A small consistent forearm uptake of 3-OHB was recorded on all occasions.

Blood concentrations of glycerol also changed in parallel with FFA: baseline (SRIF, 27 ± 7 μmol/L; SALINE, 43 ± 5 μmol/L), somatostatin infusion (SRIF, 52 ± 14 μmol/L; SALINE, 59 ± 6 μmol/L), and clamp (SRIF, 23 ± 9 μmol/L; SALINE, 23 ± 3 μmol/L). Forearm balances of glycerol remained around zero in both situations.

Comparison of arterialized vs. arterial samples

The use of arterial instead of arterialized samples did not introduce any novel differences between the two protocols.

Compared with arterialized samples, blood glucose values were consistently higher (0.06 ± 0.01 mmol/L, $P < 0.05$) in arterial blood. The somatostatin- induced augmentation of forearm glucose uptake persisted when calculations were based on real arteriovenous measurements (SRIF, 0.88 ± 0.23 mmol/L; SALINE, 0.56 ± 0.21 mmol/L, $P < 0.05$). Arterial concentrations of lactate were constantly below the arterialized levels (mean difference 108 ± 51 μmol/L, $P < 0.05$). The arterial concentrations of alanine, FFA, 3-OHB, and glycerol could not be distinguished from the concentrations in arterialized blood.

Blood flow and oxygen saturation

Total forearm blood flow remained constant at around 3.2 ± 0.6 mL/100mL (SRIF) and 3.4 ± 0.5 mL/100 mL (SALINE) in both situations (Table 1).

Similarly, oxygen saturations in arterial (SRIF, 98.1 ± 0.3%; SALINE, 98.1 ± 0.3%), arterialized (SRIF, 94.2 ± 0.7%; SALINE, 94.1 ± 0.5%), and deep venous (SRIF, 64.5 ± 3.0%; SALINE, 65.5 ± 2.6%) were stable and indistinguishable throughout both experiments.

Discussion

The present study was designed to assess any possible direct effect of somatostatin on basal and insulin-stimulated substrate balances across the perfused forearm. We found an increase of 50–60% in arteriovenous glucose differences during the clamp, clearly suggesting that somatostatin may act independently to raise insulin-stimulated glucose uptake in muscle. Furthermore, we found a small but significant decrease in circulating levels of insulin and glucagon during infusion of only 25 μg/h SRIF. This could mean that the pancreatic islet cells are more sensitive to SRIF than was hitherto assumed, but it could also merely reflect a time-dependent decrease.

The notion that somatostatin may possess extrapancreatic actions to increase glucose clearance was initially fuelled by Bergman *et al.* (6), who showed this effect in dogs despite meticulous replacement with insulin, glucagon, and GH. In line with this finding, studies in fasted dogs (8, 9) and in humans exposed to hyperinsulinemic glucose clamps (7, 10) or an insulin-infusion protocol (18) or in the basal state (19) have indicated that administration of somatostatin increases glucose turnover (8, 9), augments insulin sensitivity (7, 10), or decreases circulating glucose concentrations (18, 19). It should be noted that some of these latter studies did not replace glucagon and that none replaced GH.

On the other hand, some studies (11, 12) have failed to detect any effect of somatostatin on insulin action in healthy humans. Furthermore, experiments in which somatostatin and metyrapone were employed to clamp the actions of glucagon, GH, and cortisol during insulin-induced hypoglycemia showed that this so-called pancreatic-adrenocortical-pituitary clamp technique reproduced the spontaneous metabolic responses when counterregulatory hormones were replaced. Finally, Cherrington *et al.* (19, 20) did not find any effect of somatostatin in the perfused rat hind limb or in dogs

fasted overnight. The reason for the conflicting results regarding the impact of somatostatin on glucose homeostasis is unclear but could perhaps relate to differences in species and in the selection of somatostatin dosages, hormone replacement, and level of insulinemia. However, it should be added that the animal studies quoted above examined the effects of SRIF in the basal state, when muscle glucose uptake is very low, and that the possibility of a type 2 error cannot be disregarded entirely in some of the human studies. On the whole, it seems fair to assume that the prime reason for the disparate results in studies employing systemic infusion of SRIF and subsequent hormone replacement is the extreme delicacy with which such replacement must be carried out in order to avoid both underreplacement and overreplacement. In the present study, somatostatin was infused directly into the brachial artery, thus allowing for assessment of immediate effects on human muscle. In the control situation, somatostatin was administered iv to reproduce any systemic effects of the locally administered somatostatin. We thus obtained comparable systemic levels of all measured hormones and metabolites; nevertheless, a striking 55% increase in insulin-stimulated forearm glucose uptake was recorded.

At first glance, the SRIF dose of 25 μg/h may seem relatively high. However, it must be considered that human metabolic studies have often included systemic administration of between 1000 and 1500 μg/h SRIF (21–23), and animal studies have employed SRIF doses equivalent to human doses above 3000 μg/h (6, 8). Aiming at local forearm conditions comparable with those under a systemic infusion of roughly 1250 μg/h, and assuming a unilateral forearm blood flow of 40 mL/min or 1% of cardiac output (24), this would (from an isolated point of view) suggest the use of 12.5 μg/h in the perfused forearm. It also has to be considered that 1) the tip of the perfusion catheter is situated 10 cm above the elbow, which means that some of the administered SRIF will enter the vascular beds of the upper arm and thereby escape the forearm; 2) the combined use of the heated dorsal hand vein and the hyperinsulinaemic clamp techniques may tend to increase limb blood flow, as noted presently, and thereby dilute the administered SRIF; and 3) during perfusion with small amounts of SRIF, there is a relative deficit of recirculating SRIF compared with systemic high-dose infusion. With a dose of 25 μg/h, it may be assumed that less than one tenth of what is seen with systemic doses above 250 μg reenters the circulation for a second or third pass in the target tissues, including muscle. For these reasons, we chose a perfusion rate of 25 μg/h, which may be regarded as being within the upper range compared with more conventional experimental conditions.

Some of the studies mentioned earlier showed that somatostatin may additionally increase glucose turnover in the basal or fasted state. The present study does not entirely exclude this possibility; in the basal state, forearm uptake of glucose is very small, and subtle changes may escape detection.

What might cause the apparent insulin-potentiating effect of somatostatin? First, it is possible that somatostatin may specifically reduce muscle blood flow, thus leading to increased arteriovenous glucose differences. However, this seems implausible inasmuch as, in accordance with previous observations (25), we recorded unchanged total forearm blood flows and also because oxygen saturations in the deep venous blood draining the forearm muscles remained unaffected throughout both experimental situations.

Second, the increase in glucose uptake might be provoked by inhibition of local lipid oxidation and lead to an inverse increase in glucose oxidation, in accordance with the FFA/glucose cycle (26). Circulating concentrations of FFA are generally held to be the major determinant of FFA utilization (27), and these concentrations were similar, regardless of whether somatostatin was given systemically or locally. Although glycerol release from the forearm was not influenced by somatostatin, it is still conceivable that FFA release from the intramuscular lipid pool (28) may have been decreased because of increased reesterification of fatty acids in the triacylglycerol/FFA cycle. Previous studies showed that decreased blood levels of nonesterified fatty acid may account for the increase in glucose turnover observed in fasted dogs during systemic somatostatin exposure (8, 9). These studies showed proportionally minor changes in systemic glycerol concentrations that were compatible with increased peripheral reesterification of fatty acids.

Finally, it is possible that somatostatin may act directly on muscle cells to augment glucose uptake through primary interaction with either hormone receptors or postreceptor events.

In accordance with earlier studies, we found that samples obtained from arterialized venous blood yielded good estimates of arterial concentrations of glucose, 3-OHB, FFA, alanine, and glycerol (29–32). The observation that lactate concentrations in arterialized blood may be increased by approximately 100 μmol/L when compared with arterial blood was also noted earlier (32); possible sources for lactate production include skin, erythrocytes, and adipose tissue.

In summary, we find clear evidence that somatostatin, when administered in high doses, has hitherto unrecognized insulin-potentiating effects on glucose uptake in the forearm. Inasmuch as these results were obtained with relatively high amounts of SRIF and can be extrapolated to muscle elsewhere, they should be considered in the multitude of studies employing somatostatin for experimental manipulation, and results of investigations assuming no direct insulin agonistic of SRIF should be interpreted with caution.

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